THE ROLE OF SOVIET INVESTIGATORS IN THE DEVELOPMENT OF THE BLOOD BANK

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THE FIRST PAPER using the term "conserved blood" in the present-day sense was published by D. N. Belenki (1) of the International Clinic of the Regents of Moscow in 1928 under the title "A Simple Method for the Transfusion of Blood." This does not mean that he was the first to use preserved blood, for Bischoff (2) had used defibrinated blood in 1835, Larson (3) in 1847, Folli in 1849, and Landois (4) in 1873, but Belenki's paper did mark the beginning of a new era. Hustin (5) of Brussels must be given priority over Agote (6) of Buenos Aires for having first published results of experiments in the preservation of blood with sodium citrate, and to Weil (7) of the Memorial Hospital in New York goes the credit for first demonstrating and advocating that blood so preserved could be kept from three to five days and then given with complete safety and good therapeutic results. As early as 1902, Hédon (8) of France had separated the cells from the blood, resuspended them a few days later, and successfully used them for transfusions. Rubin (9) of New York definitely advocated the storage of placental blood in 1914. The present world-wide institution of blood banks does not, however, stem from any of these investigators. Fundamentally, it is a Russian contribution and grew from the great interest created by the early transfusions of cadaver blood.

ORIGIN OF THE USE OF CADAVER BLOOD

Professor V. N. Shamov of Kharkov (10) in 1927 became interested in the question of correcting defects in living bodies by the transplantation of tissue from the dead. He felt, as many before him had felt, that death is only the moment of dissolution of an intricate complex of mutual relations between the separate tissues of an organism, which individually retain their vitality for a varying time after the organism as a whole has ceased to function.

In the first series of investigations, Shamov and his assistant, Kostriukov, made hundreds of examinations on tissue and organs of animals from 15 minutes to 12 days after death, all the bodies having been kept at 0° C. They observed

that after 10-12 days nearly all tissue became infected and quickly deteriorated. All infection seemed to sweep outward from the abdominal cavity. The tissues farthest removed from the intestinal tract remained bacteria-free longest. If there were other foci of infection at the time of death, they, too, served as the starting points of waves of infection comparable to that from the intestine. It was observed that when the tissues were kept close to zero temperature, even the peritoneum often remained free of infection for 10 days while the brain, bone marrow, and heart blood were good after 12 or more days. At 22° C., however, only the bones and marrow were sterile after 24 hours.

Shamov concluded, therefore, that tissue from cadavers of previously healthy individuals may be used by surgeons, not only some hours but even days after death if the bodies have been kept at low temperatures.

Tests to determine the amount of vitality and potential function in large tissue masses or organs were difficult to devise and carry out. The choice of a suitable tissue to work with was a problem; *blood,* as the easiest to handle, was chosen. In 1929, a new series of experiments was set up using blood from chloroformed or strangled dogs (11). Contrary to all expectation, it was observed that such blood could be injected into other dogs with impunity. It had been thought that the blood would be flooded with bacteria and other toxic substances as a result of death and subsequent rapid autolysis of tissue.

In the first series of experiments the dogs were killed by chloroform and kept at room temperature. It was almost uniformly impossible to get sufficient blood to carry out experiments after the first four hours because of clotting. When, however, the animal was quickly strangled and immediately placed in a refrigerator, free-flowing, unclotted blood could be removed many hours afterwards. Having shown that such blood was not toxic, the next step was to test the ability of such blood to carry on the functions of whole fresh blood.

To test the vitality of the blood, another series of experiments were conducted in which blood from human cadavers was used to replenish the circulatory volume of dogs whose blood exhaustion had been raised 60 to 90 percent by repeated saline infusions and bleedings. In every case there was recovery when saline alone no longer was effective. These results left no doubt in the mind of the investigators that blood of a cadaver taken 10-12 hours after death not only retains physical properties capable of sustaining circulatory balance but also, in so far as the erythrocytes are concerned, full functional ability.

CLINICAL APPLICATION

Professor S. S. Yudin (12) of the Sklifosovski Institute and Postgraduate Medical School of Moscow, knowing of Shamov's work, waited for some time before a suitable opportunity for trying it out on a human being presented itself.

On March 23, 1930, with considerable trepidation, he transfused an engineer who had attempted suicide. Yudin used cadaver blood three days old, which happened to be at hand, and the patient recovered promptly from the effects of his hemorrhage. Six more successful trials had been made before he presented the results on September 7, 1930, before the Fourth Congress of Ukrainian Surgeons meeting at Kharkov. He felt that with the approbation of this group he might proceed with an operation which was highly distasteful in many respects to the population as a whole. In November 1932, he presented the results of his first one hundred cases. This report led to much comment (13, 14, 15) and a tremendous revival of interest in the whole field of blood transfusions. Skudina and Barenboim (16) in 1931, working under Yudin, not only repeated Shamov's earlier work but extended it to show experimentally that erythrocytes of fresh cadaver blood completely retained their ability to carry oxygen.

SPONTANEOUS FIBRINOLYSIS

In 1934, Skudina (17) noticed that the blood collected from cadavers for Wassermann tests remained liquid even after many hours. The clot formed soon after removal from the body, but 15-90 minutes later it seemed to dissolve. This was due, it was thought, to an actual lysis of the fibrin in the clot. Skudina investigated the problem further with Rusakov (1934), the pathologist of the institute. It was observed that this fibrinolysis took place only in the bloods of relatively healthy individuals who had died suddenly, e.g., following an accident or emergency operation. These changes did not take place in the bloods of those dying from chronic illnesses with cachexia and wasting, such as cancer, tuberculosis, or widespread sepsis of other types.

At the time this observation was made Yudin (18) had given about 200 transfusions with 4 percent sodium citrate as the anticoagulant. In the next 800 cases he used only bloods in which fibrinolysis had taken place spontaneously, therefore requiring no anticoagulant. The reactions in the second group were only 5 percent compared to 20 percent for those in which citrate had been used. Three factors probably played a role in this lowered figure: increased experience; elimination of possible citrate reactions when large transfusions were given; and most important, probably, spontaneous fibrinolysis. This ruled out the use of bloods from bodies of persons who had died of severe or chronic infection and of long wasting diseases.

One of the more important investigations in this series was the demonstration of a greatly lengthened clotting time in the blood of persons in severe traumatic shock by Bocharov (see Yudin, 18). It recalls the observation of Biedl and Kraus (19) in 1909 that the clotting time of the blood of dogs in anaphylactic shock increased by many minutes to many hours. Waters, Markowitz, and

Jaques (20) have suggested that the increased clotting time in anaphylactic shock is due to the rapid liberation of heparin.

Perhaps heparin is the substance in cadaver blood that prevents clotting. Since heparin is apparently thrown into circulation in increased amounts only when a person is in shock, only those persons dying acutely will have it in the blood stream. Those dying quietly from sepsis or cachexia produce no heparin in the last moments and therefore have no anticoagulant in the blood stream to prevent clotting.

FUNCTIONAL SEPARATION OF PORTAL AND CAVAL BLOOD

In the development of the technique of cadaver blood transfusions, it was observed that blood from the portal system would not spontaneously drain from a cannula in the internal jugular vein, even with the body in deep Trendelenburg position (17). The blood apparently comes only from the caval system. The blood from the mesenteric veins can be retrieved only by washing them through with saline. This is of both theoretical and practical interest because the blood in the mesenteric veins becomes infected soon after death, while that in the caval system may be infection-free days after death. In 1935 Karavanov working under Shamov (21) at Kharkov, established the fact that phagocytosis is well preserved in cadaver blood for about 11 hours after the death of an animal, then disappears rapidly.

REACTIONS

Not until 1936, eight years after the original work, were cadaver transfusions tried in Shamov's clinic. In 42 cases reported by Karavanov, Karavanov, and Perelstein (22) there were reactions in 14 percent. This is a striking figure because the senior author of that paper had reported 67 percent reactions in 102 transfusions of preserved donor blood from the same clinic the year before (23). Twenty-six percent of these reactions were severe although blood was preserved only 5-7 days. It was felt that, in addition to lessened reaction and lack of need of anticoagulant, the response on the part of the hematopoietic system of the patient was actually greater.

By 1938 Yudin (24) had done 2,500 transfusions of cadaver blood with seven deaths and 5 percent reactions. An average of 1,500 c.c. of blood was obtained from each cadaver and up to 3,000 c.c. when the portal system was washed through with saline. Yudin recommended a ten-day limit of storage since icterus followed use of older bloods. The operation in other hands has not yielded such excellent results. Arutyanian and Shevedski (25) reported observations on 52 transfusions. Blood was collected from 44 cadavers; 28 were used, 14 were un-

suitable. Thirty-two liters were obtained and in 52 transfusions there were elevations in hemoglobin of 2-14 percent and elevations of 800,000 to 1,000,000 in red blood cells. The time limit for storage was 15 days, yet in 42 accurately studied cases there were reactions in 40, or 95 percent of the cases; 14 were severe, 16 moderate, 10 slight, and only two showed no reactions.

CHANGES IN GLUCOSE, LACTIC ACID, AND PHOSPHORUS

Balakhovski and Ginzburg (26) investigated cadaver blood on the third, fourth, and sixth days from the beginning of conservation. In contradistinction to donor blood, there is a hyperglycemia in cadaver blood. This is probably due to the action of liver on glycogen after death, for hepatectomized dogs failed to show this increased glucose level. The investigators found an increase in lactic acid which at times was greater than that which could be accounted for by glycolysis alone. The authors suggested that some other process caused breakdown of gluco-protein complexes. The lactic acid content had a range of 40-60 mg. percent on the sixth day postmortem. This range was found in donor blood after 24-30 days of storage. Phosphates, likewise, were found to be increased to an average of about 17 mg. percent compared with the normal 5-6 percent. The fragility of cells was also increased.

Bocharov (27) in 1936 went into the question of the fragility more completely and concluded that every hour the blood remains in the body after death increased the fragility of the cells about 0.02-0.04, this was approximately equal to 2-3 days of conservation in a refrigerator. The reactions dropped from 25 percent to 5 percent when only bloods which had spontaneously "disagulated" were used.

Other investigators have reported similar results with cadaver blood but their findings have added nothing of outstanding merit to the fundamental work of Shamov and Yudin.

ORIGIN OF THE USE OF PLACENTAL BLOOD

There can be no doubt that priority in the use of placental blood goes to George Rubin of New York (9) who advocated it in 1914. Either his work was overlooked or the time was not ripe, for no good preservative had been demonstrated.

The first of a series of investigations to reopen this field was reported by M. S. Malinovski and his co-workers (28) in *Soviet Surgery* in 1934. In October 1936, Bruskin and Farberova (29) of the Central Oncologic Institute of Moscow reported that since June 1936, 114 transfusions of placental blood preserved 6-10 days had been administered. Their clinical work was preceded by trials on animals and laboratory investigations of the toxic and immunobiologic properties of such blood. They were able to retrieve 50-120 c.c. of blood from each placenta. They found an

average hemoglobin value of 90-120 percent, an erythrocyte count of 5,000,000 to 6,000,000, and a white blood count of 16,000 to 18,000. Citrate was the anticoagulant of choice and reactions were few.

The following year Stavskaya (30) reported a series of cases from the Mother and Child Institute of Kiev. She collected 80-300 c.c. of blood from each placenta, used 4-6 percent sodium citrate as the anticoagulant, and stored the blood for 15 days. Several observations of hers are worth noting. She stated that the blood group of the child always corresponds to the mother. This we know from the work of Smith (31) in 1928 and others is not the case. Whatever agglutinins are present at birth diminish and disappear during the first 10 days of life, after which time new agglutinins appear. This is interpreted to mean that the maternal agglutinins are lost and that the infant produces its own. Stavskaya's observation that placental blood, like certain types of cadaver blood, may be kept without preservative for 10-12 days seems to have experimental foundation in the later observations of Kato and Poncher (32) in 1940 who showed that the average prothrombin time of 100 newborn babies was 43.2 seconds and that this was gradually reduced to 25 seconds by the tenth day. This suggests that the lack of coagulation is due to prothrombin deficiency. Stavskaya also reported markedly increased potassium and calcium values for serum, demonstrated that the low level of protein was due to the globulin fraction, and that the blood was rich in estrogenic and gonadotropic substances as well as in an epinephrine-like substance.

In 1935 Kantorovich (34) advocated placental blood for massive transfusions. Subsequent investigators in considerable numbers have confirmed and extended the work of these early workers in this field.

Before Rubin's (9) paper was rediscovered there was some question as to priority in the use of placental blood. Malinovski's paper (28) undoubtedly preceded that of Goodall, Anderson, Altimas, and McPhail (33). The chief interest for us at this time lies in the fact that each of these groups of investigators, one in Russia, the other in Canada, was stimulated by the earlier work of Shamov and Yudin. A letter from Dr. Goodall to the author, dated July 7, 1939, contained the following: "I really do not know who has precedence in the matter of placental blood used in transfusions. My work was discussed among my colleagues for a year before anything active was undertaken in the matter of preservation when I got information upon the preservation of the blood of cadavers as used in the Moscow School of Haematology. At that time, we were under the impression, my colleagues and I, that blood groups were not fixed at birth, and that, therefore, newborns should be in the position of universal donors. We were disappointed to find that this was wrong and that groups were fixed at birth. All this took time. Our written work began in 1933-1934 and our work covering 300 transfusions had gone to print after correction of galley proofs before we learned that the Russians had been working upon the same problem synchronously. I do not know who has priority, and, I am

sure I speak for my colleagues when I say that it is a matter of small moment to us. The chief thing is that this work has advanced our knowledge of transfusion and given us an additional source of blood." It is the type of answer one would expect from one devoted to the scientific method in any country.

DONOR BLOOD AND THE BLOOD BANK CONCEPT

The interest aroused by cadaver blood transfusions gave the impetus which resulted in the voluntary donor blood bank. In the report of the work of the Third Congress of Russian Physiologists (1929) there were several articles showing this awakened interest in the subject. S. S. Briukhonenko and associates (see Perelman, 35) reported "certain elements which coagulate and stabilize blood in vitro and vivo." Soon afterwards, from the Central Institute of Hematology and Transfusions in Moscow a series of studies were begun under the directorship of Professor A. Bagdassarov. The first of these, reported by Perelman (35) in 1931, showed that blood kept in physiologic citrate solutions changes more slowly at 0° C. than at room temperature. Arutyanian (36) in 1932 gave transfusions of stored blood from voluntary donors and confirmed Perelman's experimental work.

Balakhovski (37) and his associates in 1932 recommended the solution of sodium citrate, sodium chloride, magnesium sulfate, and potassium chloride, which became widely known as the Russian or I.H.T. solution. They felt at that time that this solution was superior to isotonic citrate or a citrate glucose mixture. Balakhovski (26) tells us that Vlados, working in his laboratory, suggested that 6 percent citrate solutions were more effective than the physiologic solution previously used.

By 1936 Bagdassarov (43) reported the results of 6,345 transfusions; 3,304 were done at the institute itself and 3,041 at various stations in Moscow. Among these 2,790 had been preserved with 6 percent citrate, 2,074 with I.H.T. serum, and 1,481 with other preservatives, including a few of defibrinated bloods. When the original prejudice of Balakhovski had been overruled by experimental evidence showing that glucose is an excellent medium for erythrocytes and that the resulting lactic acid formation is not toxic, glucose-citrate solutions were introduced as preservatives.

About June 1932 conservation was begun at the Leningrad Institute of Blood Transfusion under the directorship of Doctor Hesse. By 1934 Filatov and Depp (38) could report 1,529 transfusions with "canned" blood. From their central station blood was being supplied at that time to 41 hospitals in the vicinity of Leningrad.

In March 1934 Tenconi and Pallazzo (39) reported from Buenos Aires their results on the first 41 transfusions of preserved blood in South America. Jeanneney and Vieroz (40) writing in the *Bulletin de la Société nationale de chirurgie* in December 1934, attribute the priority of this method to the South American investigators. This, of course, is not so as the preceding notations clearly show. Jeanneney

stated that he did not know of previous work on the storage of blood from living donors but that, in experimenting on the dog to check Yudin's results, the idea suggested itself and their first observations were reported in May 1934.

Tzanck (41), long a great student of the problem of transfusions, was late in condoning the use of banked blood but his investigations, stimulated perhaps by his skepticism, were instrumental in accurately establishing many of the changes in preserved blood. This skepticism was perhaps merited, for Karavanov (23) reported from Shamov's clinic in 1935 that there were 67 percent reactions, 25 percent of which were severe, where blood only seven days old had been used. Filatov (38) in 1935 reported reactions in 50 percent and four deaths in the first 659 transfusions, while Grozdov (42) had reactions in 41.2 percent of 142 transfusions. As in any new departures, results were not too good at first. Bagdassarov (43) in 1937 reported his results in four series of patients to whom over 6,000 transfusions had been given. He noted reactions in 62 percent when I.H.T. serum was used, in 62 percent with glucose-citrate solution, in 65 percent with 6 percent citrate, and in 89 percent with 3.8 percent citrate.

Gnoinski (44), director of the Biologic and Hematologic Laboratory of the Red Cross Hospital at Varsovie, gave preserved blood its severest test. In 1938, after man-dog experiments, he gave blood which had been preserved in 6 percent sodium citrate for 66, 64, 66, 69, 66, 64, 66, and 84 days, respectively. In each case there was a sharp rise in temperature; in most, severe chills; in four, increased urobilinogen; in four, hemoglobinuria; and in three, severe pain with dyspnea. All recovered and all showed improvement in the blood picture. The average amount of blood given was 280 c.c. From this experience he concluded that preserved blood was innocuous and of great therapeutic value.

In August 1936, Duran Jordá (45), organized for the Republican Army of Spain, under the name of the Barcelona Blood Transfusion Service, the best system of collection and distribution of blood devised up to that time. The service at one time had immediate access to 28,900 donors and distributed over 9,000 liters of blood before Franco's victory. The hermetically sealed containers were of an advanced design and contained blood from a pool of similar types under a pressure of two atmospheres. The blood ready for use was delivered to the front in refrigerated trucks or train cars. Jordá used a citrate-glucose mixture (1 percent glucose, 4 percent sodium citrate).

In the United States during the years 1925 to 1935, while many individuals undoubtedly took blood from donors and saved it until some time later before giving the transfusion, no organized storage and distribution was noted until about 1937. In a survey of blood transfusion in America by Levine and Katzin (46), which appeared in 1938, no mention is made of preserved blood in any form.

In March 1937, Fantus (47) instituted at the Cook County Hospital in Chicago a system built around the principle of having a central depot in the hospital where

donors could be sent to have blood drawn and stored for future use. He called this system a "blood bank" and soon afterwards the words were like magic on the tongues of the populace.

All of the findings which the Russian investigators reported have not been confirmed. To them, however, must go the credit for supplying the early work, most of the fundamental knowledge, and the impetus which has to a large degree been responsible for the widespread creation of the blood and plasma banks which have played and are playing such a tremendous role in reducing the number of deaths on the battle fields of the world.

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